SIR WILLIAM MACLEAY MEMORIAL LECTURE, 1966

THE CENTENARY OF MENDEL

D. G. Catcheside

John Curtin School of Medical Research, Australian National University, Canberra

[Delivered 15th July, 1966]

Mendel, the centenary of whose work is the subject of this Sir William Macleay Memorial Lecture, had the unusual distinction of originating a new branch of science. Generally, in the development of science, a new advance depends on many predecessors whose work provides a basis for it. Genetics is an exception, owing its origin to one man, Gregor Johann Mendel, who expounded its principles at Brno in two lectures on 8th February and 8th March, 1865. His work made scarcely a ripple in the tumultuous sea of biological study, so stirred by the tidal waves of Darwinism in 1859. It was forgotten for the next 35 years, barely even noticed and certainly not understood. Mendel had no authority as a biologist and the very merits of his work, as we see it, must have made it suspect at the time and seemingly the work of an eccentric. Even the very simplest mathematical practices, beyond mere measurement, had found no place in biology.

A predecessor is a man who, at an earlier date, makes a discovery which his successor is able to enlarge into a general principle of universal validity. In this sense Mendel had no predecessors. There were many breeders who hybridised different species and varieties of plants and domesticated animals. However, the objectives they were studying do not really constitute basic genetics and claims that any of them had anticipated Mendel do not bear inspection. They were studying hybridism, whether sterility in a hybrid was due to the pollen parent or to the seed parent, whether either parent could be held responsible for the characters of different parts of the plant, which parent had prepotency in determining the characters of the hybrid, whether the parents were different species or merely varieties. Thus Colladon in 1822 was led to conclude that grey and white mice were different species ! Generally, the parents used by the early hybridisers in their experiments were either different species or else varieties differing in many characters. The results obtained were chaotic and often inconstant or contradictory. They led to no general principles. This was the difference between previous attempts to study heredity and the revolution effected by Mendel.

The failure of his contemporaries to recognise the significance of Mendel's work confirms that there were no minds already prepared to see that the problem of heredity had been laid bare to complete solution. None saw that Mendel's researches supplied what he, rightly, considered to be missing from Darwin's theories, namely a mechanism of heredity and of the conservation of heritable variation. Indeed, the influence of Nägeli, interested in the same trivialities as the early hybridisers, led Mendel to fruitless and exacting work in hybridising hawkweeds, now known to lack sexual reproduction.

No earlier work anticipates Mendel's reduction of the problem of heredity to the study of single character differences which result, after crossing, in hybrid offspring in certain specified proportions. Goss, indeed, working also with garden peas, had observed dominance, recessiveness and segregation, going so far as to count the numbers of the different kinds in the F_2. Likewise, Darwin observed these features in snapdragons. Neither arrived at any general principles as a consequence.

Mendel, in writing about previous work, clearly stated his new scientific procedures as follows: " . . . among all the numerous experiments made, not one has been carried out to such an extent and in such a way as to make it possible to determine the number of different forms under which the offspring of hybrids appear, or to arrange these forms with certainty according to their separate generations, or definitely to ascertain their statistical relations ".

The constancy of characters of hybrids, as Mendel explained, was the starting point of his work. It enabled him to postulate an explanation of his results by supposing that the characters were each determined by particulate factors, that the factors from each parent segregated completely at the formation of the germ cells and in equal numbers, and that there were equal chances of fertilisation of germ cells bearing either one of the two different factors, which thereby became recombined. In fact, Mendel made scarcely any distinction between the unit characters visible in the adult organisms and the unit factors borne in their germ cells, using the word *Merkmal* for both and treating them as a virtual identity. He left out everything that comes between them, how one determines the other, the whole of development. Knowledge of the connections is immaterial to an understanding of heredity.

Statistical analysis of Mendel's data led Fisher, in 1930, to conclude that Mendel knew what proportions to expect when he made his experiments. This means that he had thought out his scheme of particulate inheritance beforehand, as an abstract and simple combinatorial exercise, before putting it to the test. It was not an empirical discovery subsequently processed by induction into a scheme. Curiously, in reporting his work to the Natural History Society in Brno, Mendel presented the data at the first lecture and the mathematical explanation at the second one.

The statistical evidence is that Mendel's data agree much better with expectation than can reasonably be expected. Taken together, the figures published by Mendel would be expected to be equalled or improved upon, in their agreement with expectation, only once in 8,000 trials. There is no question of attributing deliberate falsification to Mendel or to his assistants, to whom Mendel's expectations would have been known. But enthusiastic amateurs are prone to give an experiment the benefit of a doubt, and to bias results unintentionally by discarding poor specimens and doubtful cases, to count a portion of a sample, stopping when the proportions are " good ", thus making honest mistakes. Perhaps, indeed, Mendel did observe just this unusually consistent set of data. The conclusion that Mendel's work stemmed from an idea, worked out theoretically as a mathematical exercise, is supported by the very thorough manner in which Mendel expressed his system in mathematical terms and in a general form for universal application.

All of the main features of Mendel's theory would follow from the simplest possible assumptions of particulate inheritance. To conceive this simple hypothesis is exactly what Mendel, failed twice in an examination to qualify as a high school teacher, appears to have done. Moreover, the experiments to test the theory were performed with the most meagre facilities, a garden 35×7 metres, a few varieties of the garden pea (*Pisum sativum*), some forceps and bags to exclude insects from the flowers.

Mendel's theory could hardly have been formulated without some knowledge of the facts of fertilisation, that one egg and one sperm unite to form the zygote. This became known only a few years before his work and was not generally accepted even then. Thus Darwin thought more than one sperm was needed for each egg, both in animals and plants.

Direct observations of fertilisation were dependent upon the development of compound microscopes. Amongst lower plants fertilisation was observed in *Fucus* by Thuret in 1853, in *Oedogonium* by Pringsheim in 1856 and in fungi by De Bary in 1861. The role of the nucleus in fertilisation and cell division

was established by the work of Hertwig in 1875 on the fertilisation of the egg of the sea urchin. In seed plants, Amici in 1823 observed the production of the pollen tube, which he traced in 1830 to the ovary and even to the micropyle. In 1846 he showed, in orchids, that a cell, already present in the ovule and inactive until the pollen tube arrives, then develops into the embryo. This was confirmed and extended by Hofmeister. Hence Mendel could state " In the opinion of renowned physiologists, for the purpose of propagation one pollen cell and one egg cell unite in Phanerogams into a single cell, which is capable by assimilation and formation of new cells, of becoming an independent organism ". However, this opinion was not generally accepted. Naudin (1863) repeated experiments of Kölreuter and Gärtner, placing counted numbers of pollen grains on stigmas and concluding that a fully viable seed required more than one grain. Mendel himself repeated this experiment, using *Mirabilis* as had Naudin, and found, as he wrote in a letter to Nägeli, that a single grain was sufficient.

The foundations of our knowledge of chromosomes, mitosis and meiosis were laid between 1882 and 1885 ; Mendel died in 1884. Roux published a remarkable essay in 1883 in which he argued that the linear structure of the chromosomes and their precise longitudinal division were such striking and universal phenomena as to indicate selective value. He suggested that this lay in their effectiveness in assuring that each daughter cell received the same complement of chromosomal material. Further he regarded this as a strong argument for identifying the chromosomes as the bearers of the units of heredity. These units were here for the first time specified as being arranged in a linear series. We have no information as to whether Mendel himself considered his different pairs of factors as being other than independent from one another.

In discussing the centenary of Mendel's work, it has been proper to consider what Mendel did discover, how he did it and how he proved his theory. But my main purpose is to give some account of where genetics has now reached and the paths by which it has advanced. However, the advance has been so fast and so far that it is impossible to do justice to all of it. Particular attention will be paid to the nature of the hereditary factors and how they act, with a glance at possible future advances.

The rediscovery in 1900 of Mendel's work, independently by Correns, Tschermak and de Vries, was rapidly followed by evidence of its universal applicability to all organisms as a strong probability. About a quarter of a century or so later this evidence was extended to microorganisms, first to fungi and algae and later to bacteria and viruses. These extensions have resulted in remarkable advances in knowledge at an unprecedented rate.

Early this century sex linkage, linkage and gene interaction were found as exceptions to the simple Mendelian rules. Polysomic inheritance, the effect of structural changes (such as interchanges, inversions and deletions) led to proofs that the chromosomes, visible microscopically, were the bearers of heredity. Probably the most fundamental of these discoveries was linkage. Many factors were found to be correlated in their segregation, rather than independent as Mendel's Second Law states, with recombinants being in a minority. All experiments have agreed with the hypothesis that the factors belong to a number of distinct linkage groups and that those in a linkage group are arranged in a linear array. The hereditary material, which carries the factors or is composed of them, is filamentous.

The name ' gene ' was introduced and used in the sense of Mendel's factors in the germ cells. Genes were defined physiologically, namely that there is a heritable factor capable, under suitable circumstances, of being expressed as a recognisably distinct character. However, a gene responsible for a given character is detectable, in general, only if some other individual organism has

a different, alternative gene responsible for a difference in the character. These two genes are allelic genes. Alleles form a set of genes all affecting one function in various ways.

Whether two gene changes (mutations) are allelic or not is generally settled by the coupling and repulsion test, now often called the *cis-trans* test. Such changes in nomenclature, and there are many, as often reflect an ignorance of earlier knowledge as a radically changed point of view. Almost all mutational changes from the normal involve loss or partial loss of some characteristic. When combined with the normal, as a diploid in an animal or higher plant or in a yeast or as a heterocaryon in *Neurospora* or as a mixed population of bacteriophages growing in a bacterium, the mutant type is hidden by the normal. The normal is commonly dominant to the mutant which is recessive : it is as though the presence of a function in one covers up its absence in the other.

Thus the problem of defining a gene as a unit of function is essentially that of deciding whether any two mutants are different changes of the same normal gene or changes of two different genes. If the same function were lost in both mutants, there would be no gain of function by their combination in a diploid or a heterocaryon. However, if different functions were lost in each mutant, the two would be able to complement each other's loss, so restoring function. Thus with mutational changes in nonallelic genes, the coupling and repulsion phase heterozygotes both possess the normal function. However, with mutational changes in allelic genes, the repulsion phase heterozygote appears mutant whereas the coupling phase appears normal.

In various microorganisms, it has been shown that, if a large number of mutants are tested in pairs, they are divisible into a number of groups, such that complementation always occurs between members of different groups. Within groups, either no complementation occurs between any pair or no complementation occurs between some of the individuals and all other members of the group, some pairs of which complement. In the latter case, the class of noncomplementing members holds the group together. The genes responsible for differences within a group are allelic while those responsible for differences between groups are nonallelic. The significance of complementation between alleles will be mentioned later.

The differences between alleles, defined physiologically, are usually capable of genetic recombination. This has been demonstrated in *Drosophila*, maize, various fungi, bacteria and bacteriophages. Different pairs of alleles show different frequencies of recombination and these frequencies have been used to construct fine structure maps on the principle that the sites of mutation should be linearly arranged, with the frequency of recombination a function of the distance between them.

The clearest and most extensive evidence is drawn from studies of the *rII* genes of the bacteriophage T4. Here proof of the linearity is based on topological criteria rather than the statistics of recombination. Some *rII* mutants show no recombination with others, which themselves are able to recombine. The former can be regarded as more extensive abnormalities than the latter and may be deficiencies of various parts of the *rII* genes. If a series of them are analysed, some pairs showing recombination and others not, the results can be arranged in a matrix which can be represented as a linear map with the defects of the mutants extending over segments of various length. The overlaps define a unique order and none of the information requires the map to have more than one dimension. The total number of sites at which mutation has been shown to occur in *rII* exceeds 300, a value which probably represents little more than a third of the possible sites.

Thus, the heritable material is filamentous and is segmented into genes, distinguished by their functions. What are their functions? How do they

act? Of what are they made? What separates them? These are not independent matters, but certain functions were discovered first. Garrod, then Regius Professor of Medicine at Oxford University, suggested in 1909 that the function lost in a mutant was the ability to make a simple chemical transformation and that this was because of the loss of a specific enzyme. Hence, the proposition that each normal gene determined a specific enzyme. Garrod's theory was based upon the study of inborn errors of metabolism in man such as the failure in alcaptonuria to break down homogentisic acid and the failure in phenylketonuria to oxidise phenylpyruvic acid. Each of these metabolic defects is inherited as a simple recessive.

This gene-enzyme theory was ignored for more than 30 years. In the meantime, Beadle and Tatum had made the same proposal in 1941 and were able to obtain a large series of biochemical mutants in the fungus *Neurospora*. Some of these mutants provided the first evidence of definitive changes in the properties of specific enzymes accompanying alterations in specific genes. Later it was shown that gene mutation was associated with changes in the composition of the protein of which enzymes are composed. Gradually, through the application of analytical procedures suitable for small amounts of complex materials, mainly due to advances in chromatographic separation of amino acids and peptides, it was shown that a given protein is made up of a particular number of amino acids arranged in a precise sequence. It was shown also that the corresponding proteins, determined by heritable differences, may differ merely in the substitution of one amino acid for another at a definite place in the sequence. This was first shown for haemoglobin in man by Ingram in 1957, and has been extended to other systems, especially in bacteria and bacteriophages, by many workers. Among them, Yanofsky has shown, for the A protein of tryptophan synthetase in *Escherichia coli*, that the order of sites of allelic difference in the gene map parallels the order of positions of amino acid substitution in the protein specified by the normal gene at the locus. Another demonstration of this parallelism, or congruence, due to Brenner and his associates, is dependent upon the fact that some kinds of mutation result in the formation merely of fragments of the normal protein. In bacteriophage T4, they were able to show a strict correlation between the position of the mutant site in the gene map and the length of the peptide formed and so the position of discontinuity with reference to the normal polypeptide.

Questions left to answer at this stage include how the gene determines the protein, how the gene duplicates and what is the chemical and physical nature of the gene. It was a major achievement of the combined use of genetical and cytological methods to demonstrate that the chromosomes were the site of the genes. Further it was possible to demonstrate that there is a congruence in order of the genes in a linkage map and of the order of parts of a particular chromosome. Here it is reasonable to assume a collinearity in the sense that genes are parts of chromosomes, or of a constituent. The chromosomes were found to be composed of deoxyribonucleic acid (DNA), ribonucleic acid (RNA) and proteins, mostly basic ones. Amongst these materials, only the DNA was in constant quantity from cell to cell of an organism, doubling before each mitosis. This was circumstantial evidence for DNA being the heritable material, but there was some reluctance to accept that it could show enough variety to be genetic, especially as it was thought to be merely a repeating sequence of the four nucleotides. At the same time most of the protein of the chromosomes appeared equally monotonous, but some hope was centred in the small amounts of acidic protein present.

Clear evidence for DNA being the genetic material of bacteria and of bacteriophages came first from the demonstrations that it was the material of transformation in *Pneumococcus* and virtually the only material injected by phages into host bacteria. In the meantime, DNA and RNA were subjected to thorough chemical study, so that by 1951 Todd and Brown had established

in detail the structure of nucleosides and nucleotides and how they were linked together in nucleic acids to form linear molecules in which nucleotides are joined together by phosphate links to the 3 and 5 positions of their sugar residues. X-ray diffraction studies of DNA fibres enabled Wilkins to establish the constancy of pattern and approximate dimensions. Improvements in analysis of DNA from many sources resulted in the discovery of variations in the amounts of the four nucleotides, but with certain regularities, especially equivalence in the amounts of adenine and thymine and of guanine and cytosine, respectively, among the bases.

To account for these data, Watson and Crick in 1953 proposed that DNA consists of two spiral polynucleotide chains, relationally coiled about one another and joined by hydrogen bonds between their bases. This structure is now generally accepted as correct in principle, subject to refinements in details of bond angles and atom spacing. Besides suggesting how the molecule might replicate and preserve the same genetic information in the daughters, it provided a mechanism of mutation and suggested how the information in the DNA might be related to that in the polypeptide of a protein.

The double spiral structure predicts a semi-conservative mode of replication. Meselson and Stahl showed this to occur in the replication of DNA in *Escherichia coli* by following the distribution of heavy isotopes of nitrogen and carbon in the DNA of progeny developing in the presence of normal isotopes. Similar observations have been made with an alga and with mammalian cells. Labelling experiments to study the replication of chromosomes, in higher plants showed a similar semi-conservative process, but further work has disclosed complexities. Labelling experiments with the chromosomes of bacteria have also shown a semi-conservative process and, in addition, that the chromosomes are circular and are replicated sequentially starting from a particular site.

How is DNA related to protein? These are two filamentous materials, one composed of four different members (the nucleotide pairs), the other of about 20 (the amino acids). It appeared possible that the relation was analogous to two different codes, one with four and the other with 20 symbols, for the same information. Obviously a one to one or a two to one relation gives insufficient scope. The least proportionality likely is a three nucleotide pair to one amino acid relation. It is unlikely that the code could be mixed, since it would require commas between the elements of the code as well as stops at the ends of the section of DNA specifying one protein. Also, it is unlikely that the code is overlapping, since then several adjacent amino acids would generally be affected by one mutation. The triplet code provides 64 symbols, some of which represent signals other than amino acids. Moreover, it has been found that some amino acids are represented by more than one triplet, a degeneracy of the code.

The three to one relation was established for bacteriophage by ingenious experiments of Crick, Brenner and their associates. It was thought that certain mutants, induced by acridines, were due to the addition or subtraction of base pairs. Some reversions of these might have compensatory subtractions or additions near, but not at, the original mutant site. These suppressor mutations were separated and found themselves to be mutant. Whether base pairs were added or subtracted could be defined in terms of a standard. When three additive mutants, or three subtractive mutants, were put together the strain was approximately normal, rather than mutant, provided the sites of the mutants were fairly close together with specified parts of the gene.

The significance of a third important constituent of living matter, RNA, became clear through a different sequence of events, particularly through the efforts of biochemists to determine the mechanism of protein synthesis. It is not necessary to go into details. In essence, it is now fairly well established that an RNA polymerase catalyses the synthesis of specific RNAs by transcription from segments of the DNA, so that the sequence in a given RNA is

the complement of the sequence in the strand of DNA copied. There are three classes of RNA molecules: (1) two species of ribosomal RNA (rRNA), one about 1,500 and the other 3,000 nucleotides long, that form parts of the structure of the ribosomes concerned in protein synthesis; (2) several dozen species of transfer RNA (tRNA), each about 100 nucleotides long, that provides adapters for the amino acids joined in protein synthesis; (3) hundreds of thousands of species of messenger RNA (mRNA), of diverse lengths, perhaps ranging up to tens of thousands of nucleotides, that provide the templates for orderly polymerisation of amino acids into specific polypeptides. Thus some genes determine only RNA (rRNA and tRNA) but most are expressed as protein. Each species of transfer RNA becomes coupled to a specific amino acid and the latter is led to its proper position in the amino acid order by a specific triplet in the tRNA complementary to a triplet in the messenger RNA.

The discovery that polyribonucleotides stimulate the incorporation of amino acids in cell free systems able to synthesise proteins, led very quickly to solutions of which nucleotide triplets correspond to each amino acid. This was achieved by using synthetic polynucleotides composed either of single nucleotides or of random mixtures of two or more in various proportions. Of course, the information is incomplete and it is not yet known exactly how many of the 64 triplets do code for amino acids. Some triplets do not code for any amino acid and these have been referred to as nonsense triplets. In fact this is an unsuitable name, since at least some of them serve a special function in information transfer. In bacteria and bacteriophages, it has been shown that some mutations result in the termination of synthesis of a polypeptide so that only a fragment of the normal one is formed. Termination occurs because the mutation has resulted in triplet which signals that this very event should occur. The evidence is strictly genetical, dependent upon the demonstration that a distinct suppressor mutation may allow an amino acid to be inserted despite that the signal normally leads to the cessation of amino acid polymerisation.

Thus we have a strictly mechanistic theory of gene structure, function and replication. The gene is a sequence of nucleotide pairs, presumably a multiple of three in number. The gene replicates by enzymic processes and is transcribed into RNA by another enzymic process. Most species of RNA provide templates, when wound on a number of ribosomes, for ordering specific transfer RNAs, to which are coupled acylated amino acids, which can then be bound together in an order, specified by the messenger RNA. The polypeptides so formed fold to form proteins, generally enzymes. Many enzymes are composed of several similar protein units and in these cases some defective allelic mutants may complement in a hybrid enzyme by allosteric correction of folding errors in the mutant proteins.

The theory is further that there is a gene or a complex of genes for each and every function in an organism. This is substantiated by the discovery of genes for each enzyme of intermediary metabolism, of genes for some parts of the machinery of protein synthesis, of genes for a wide variety of morphological, physiological and behavioural characters, of genes for behaviour of constituents of cells, especially the chromosomes and mitochondria, and of genes controlling the action of other genes.

Genetics is a powerful method of biological analysis, discovering principles and mechanisms by analysis of numerical data of the distribution of heritable differences amongst progeny. In essence its principles extend from bacteriophage to man; it unifies biology. It may be expected soon to make decisive contributions to some of the outstanding fundamental problems in biology, such as the mechanisms of genetic recombination, differentiation and behaviour.

Mendel did indeed give us a legacy, one I am sure Sir William Macleay would appreciate were he alive today to see how genetics has made such good intellectual use of the bacteria, whose general study he fostered. I am grateful for the opportunity afforded of paying respectful tribute to both these benefactors.

Bibliography

General references

The following deal with broad aspects of the subject and contain references to nineteenth century work—

Iltis, H., 1924.—" Gregor Johann Mendel, Leben, Werk und Wirkung ". (Springer, Berlin). English translation, E. and C. Paul, 1932, " Life of Mendel ". (W. W. Norton and Company, New York).

Roberts, H. F., 1929.—" Plant Hybridization before Mendel ". (Princeton University Press, Princeton, N. J.).

Sachs, J., 1875.—" History of Botany ". Translated by H. E. F. Garnsey, 1890. (Oxford University Press, Oxford).

Sturtevant, A. H., 1965.—" A History of Genetics ". (Harper and Row, New York).

Wilson, E. B., 1896.—" The Cell in Development and Heredity ". (Macmillan Co., New York). Second edition, 1900 ; Third edition, 1925.

Zirkle, C., 1935.—" The Beginnings of Plant Hybridization ". (University of Pennsylvania Press, Philadelphia).

Special references

Beadle, G. W., and Tatum, E. L., 1941.—Genetic control of biochemical reactions in *Neurospora*. *Proc. nat. Acad. Sci.*, 27 : 499–506.

Benzer, S., 1961.—On the topography of the genetic fine structure. *Proc. nat. Acad. Sci.*, 47 : 403–415.

Brenner, S., 1966.—Collinearity and the genetic code. *Proc. roy. Soc.*, B164 : 170–180.

Brown, D. M., and Lythgoe, B., 1950.—Deoxyribonucleosides and related compounds. Part II. A proof of the furanose structure of the natural 2-deoxyribonucleosides. *J. chem. Soc.*, 1990–1991.

Crick, F. H. C., Barnett, Leslie, Brenner, S., and Watts-Tobin, R. J., 1961.—General nature of the genetic code for proteins. *Nature*, 192 : 1227–1232.

Correns, C., 1900.—G. Mendel's Regel über das Verhalten der Nachkommenschaft der Rassenbastarde. *Ber. deutsch. bot. Gesells.*, 18 : 158–168. English translation 1950, in The birth of genetics. Suppl. *Genetics*, 35 : 33–41.

————, 1905.—Gregor Mendel's Briefe on Carl Nägeli, 1866–1873. *Abh. math.-phys. Kl. Kön. Sächs. Gesellsch. Wiss.*, 29 : 189–265. English translation, 1950, in The birth of genetics. Suppl. *Genetics*, 35 : 1–29.

De Vries, H., 1900.—Sur la loi de disjonction des hybrides. *C. R. Acad. Sci.* (Paris), 130 : 845–847. English translation 1950, in The birth of genetics. Suppl. *Genetics*, 30–32.

Fisher, R. A., 1936.—Has Mendel's work been rediscovered ? *Ann. Sci.*, 1 : 115–137.

Garrod, A. E., 1908.—Inborn errors of metabolism. *Lancet*, 2 : 1–7, 73–79, 142–148, 214–220. Published separately as a book, 1909. (Oxford University Press, London).

Ingram, V. M., 1963.—" The Hemoglobins in Genetics and Evolution ". (Columbia University Press, New York).

Lythgoe, B., and Todd, A. R., 1947.—Structure and synthesis of nucleotides. *Symp. Soc. exp. Biol.*, 1 : 15–37.

Mendel, G., 1866.—Versuche über Pflanzenhybriden. *Verh. naturforsch. Ver. Brunn*, 4 : 3–47. English translations, 1901. *J. roy. hort. Soc.*, 26 : Bateson, W., 1909, 1913. " Mendel's principles of Heredity ".

Meselson, M., and Stahl, F. W., 1958.—The replication of DNA. Cold Spring Harbor Symp. quant. Biol., 23 : 9–12.

Tschermak, E., 1900.—Über künstliche Kreuzung bei *Pisum sativum*. *Ber. deutsch. bot. Gesells.*, 18 : 232–239. English translation 1950, in The birth of genetics. Suppl. *Genetics*, 35 : 42–47.

Watson, J. D., and Crick, F. H. C., 1953.—The structure of DNA. Cold Spring Harbor Symp. quant. Biol., 18 : 123–131.

Yanofsky, C., Carlton, B. C., Guest, J. R., Helinski, D. R., and Henning, U., 1964.—On the colinearity of gene structure and protein structure. *Proc. nat. Acad. Sci. U.S.*, 51 : 266–272.